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Etanercept

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Etanercept is a recombinant molecule consisting of the extracellular domain of the tumor necrosis factor-alpha (TNF-alpha) p75 receptor fused to the inert FC portion of IgG1 molecule. The dimeric nature of etanercept permits binding of the protein to two free or receptor bound molecules of TNF-alpha at an affinity 50 to 1000 times that of soluble monomeric forms of the TNF-alpha; receptor. In contrast with anti-TNF antibodies, etanercept does not induce complement mediated TNF-alpha cell lysis in vitro. This agent modulates biologic responses regulated by TNF-alpha a pro-inflammatory cytokine involved in the pathogenesis of psoriasis. Several studies demonstrated efficacy and tolerability of etanercept administered twice weekly by subcutaneous injections in patients with moderate to severe psoriasis and/or psoriatic arthritis refractory to conventional therapies. Starting from 2003, more than 250 patients were treated in clinical trials at the Department of Dermatology, University of Rome Tor Vergata, confirming that etanercept is a highly effective and safe treatment for patients affected by moderate-to-severe plaque psoriasis and psoriatic arthritis, as it reduces patients disease activity, increases functional capacity and improves quality of life. Moreover, the use of a high-dose regimen or long-term therapy can improve, in selected cases, clinical results. Mean time to relapse following etanercept withdrawal was observed approximately 4 months after discontinuation, however, PASI 75 responses were re-obtained after re-treatment. In addition we observed that etanercept is an effective and well-tolerated agent also for the treatment of childhood psoriasis and in patients with erythrodermic or pustolar psoriasis.

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Efficacy and Safety in the Long-Term Treatment with Infliximab of Psoriasis and Psoriatic Arthritis

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Effective therapies without significant long-term toxicity are needed for the chronic course of psoriasis. Infliximab is a a chimeric anti-tumor necrosis factor-alpha monoclonal IgG1 antibody that binds with high affinity and specificity to TNF-alpha; and neutralises its biological activity. Currently it is approved for the treatment of chronic diseases characterised by TNFalpha-mediated inflammation such as rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthitis and more recently for psoriasis. In recent clinical studies, infliximab was effective and generally well tolerated in patients with moderate to severe psoriasis or psoriatic arthritis. We performed an open-label clinical trial with infliximab at weeks 0, 2 and 6, followed by maintenance every 8 weeks. Evaluations were at baseline, week 22, at 1 year and at 2 years. Primary efficacy end-points were >75% improvement of PASI (PASI 75) in the plaque-type patients and changes from baseline in the health assessment questionnaire (HAQ) in the arthropatic patients. A total number of 163 patients were treated (85 patients affected by plaque-type psoriasis and 78 patients affected by psoriatic arthritis). At the present moment, 145 patients have reached the 22nd week of treatment, 97 patients have reached 1 year of treatment and 50 patients have reached 2 years of treatment. Results are being discussed. No serious adverse events or delayed hypersensitivity reactions were noted. Our experience seems to indicate that Infliximab is an effective and safe therapy for the long-term treatment of psoriasis and may have a lower incidence of side effects than traditional systemic anti-psoriatic therapies.

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Efalizumab

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Psoriasis is a common immune-mediated disease associated with significant psychosocial morbidity and a decrease in patients health-related quality of life. Efalizumab is a recombinant humanized, monoclonal IgG1, antibody approved for the treatment of chronic moderate-to-severe plaque psoriasis. Efalizumab binds to CD11a, the alpha subunit of LFA-1, inhibiting T-cell activation, cutaneous T-cell trafficking and adhesion to keratinocytes. Numerous randomized, double-blind, placebo-controlled trials confirmed the efficacy and safety of 12 weekly doses of s.c. efalizumab 1.0 mg/kg/wk in patients with moderate-to-severe psoriasis (PASI ≥12 and BSA ≥10%). On day 84, 31% of patients who received efalizumab demonstrated ≥ 75% improvement in PASI relative to baseline as compared with 4% of placebo-treated patients. In addition, 54% of patients undergoing efalizumab treatment had 50% PASI improvement as compared with 14% receiving placebo. In addition, a significant improvement of Overall Lesion Severity, Physician Global Assessment and patient's quality of life was observed. Extending treatment from 12 to 24 weeks both maintains and improves the initial response achieved at 12 weeks. Efficacy and safety of long-term efalizumab therapy has been also examined in a 36 month clinical trial which demonstrated ≥75 PASI improvement in 73% of patients. The most frequent side-effect was a flulike syndrome, which in most cases was reversible after the 3rd injection. No increased incidence of neoplasia, infections, arthritis and hematologic disorders have been registered so far. In conclusion, efalizumab is well-tolerated, safe and allows a long-term treatment, improving patients' overall quality of life.

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The use of Biologics in the Treatment of Skin Cancers

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Biologics are a set of different engineered proteins used to modify immune reactions. Their use in immune-mediate dermatoses has been proposed and validated because of their effects on defined pathophysiological pathways that regulate pivotal immunological processes such as lymphocytes activation, interaction with antigen-presenting cells and endothelial cells and production and action of cytokines and chemokines. In contrast to general immunosuppressants, they do not affect the entire immune system or have significant end-organ toxicity. Even though a past positive history for internal as well as cutaneous neoplasm is considered a specific contraindication to their use and the risk of opportunistic neoplasm is still matter of debate, some biologics directed to normal as well as malignant cells are successfully proposed in selected fields of dermato-oncology. In particular, cutaneous T-cell lymphomas served as a paradigm for the development of biological agents. In particular, Alemtuzumab, anti-CTLA-4 monoclonal antibody, rituximab, different cytokines (rIFN, rIL-2, immunotoxin conjugate denileukin diftitox, IL-12), some of them investigational, have been tested in dermatology. Alemtuzumab, an anti-CD52 humanized monoclonal antibody, and immunotoxin conjugate denileukin diftitox, have been demonstrated to be successful in advanced cutaneous T-cell lymphomas (mycosis fungoides/Sezay syndrome, CD30-negative CD8-positive cytotoxic large T-cell lymphoma, subcutaneous T-cell lymphoma). Rituximab, a chimeric anti-CD20 monoclonal antibody, has been demonstrated to be highly effective against indolent and aggressive B-cell non-Hodgkin's lymphomas. Recombinant IFN and rIL-2 have been variously included as adjuvant therapy and combined immune-therapy for high risk and metastatic melanoma patients. Their use, efficacy and incidence of adverse events are reported and discussed.